wherein the membrane is permeable to the prodrug molecules, the cytochrome P450 gene and the cytochrome P450 expressed by the gene are retained within the capsule and the prodrug molecules are converted into active drug molecules by cytochrome P450 and thereby ablate the tumor cells.

Applicants have provided an enabling disclosure for the subject matter of Claim 10, particularly as amended.

Rejection of Claims 1-4, 6-9, 15-19, 21 and 22 under 35 U.S.C. §103(a)

Claims 1-4, 6-9, 15-19, 21 and 22 are rejected under 35 U.S.C. §103(a) "as being unpatentable over of Tai et al (FASEB Journal 7: 1061-1069, 1993) and Merten et al. (Cytotechnology 7(2): Abstract, 1991) in view of Wei et al. (Human Gene Therapy 5: 969-978, 1994)" (Office Action, page 5). After, consideration of Applicants' statements in the previously filed Amendment, the Examiner states that "applicant fails to consider the combined teachings of the reference cited herein in entirety" (Office Action, page 6). The Examiner states that Tai *et al.* teach that "sustained delivery of the desired gene product in vivo can be achieved by encapsulating the genetically modified cells in a biocompatible membrane"; that "microencapsulation delivery overcomes problems associated with somatic gene therapy such as the inability to achieve gene transfers, obtaining sustained level of expression of the transfected gene and the necessity to avoid immunorejection after transplantation"; and "the use of an alginate-poly-L-lysine semipermeable membrane provided a microenvironment that was physiologically compatible with the growth of the modified cells and allowed easy diffusion of the secreted gene products without compromising the immunoisolating properties of the membrane" (Office Action, page 6). The Examiner states that Merten *et al.* teach "a method for encapsulation of mammalian cells using capsules comprising cellulose sulphate and poly-dimethyl-diallyl-ammonium chloride" (Office Action, page 6). The Examiner states that Wei *et al.* teach "genetically engineered mouse fibroblasts that produces Cytochrome P450"; that "cytochrome P450 2B1 activates inert prodrug, CPA into its cytotoxic metabolites"; and that "transplantation of cytochrome P450 2B1-producing fibroblasts followed by CPA administration, prevented meningeal neoplasia and led to partial regression of parenchymal solid tumors in the brains of athymic mice, previously seeded with rat C6 gliomas" (Office Action, page 6).

It is the Examiner's opinion that "it would have been obvious to one of ordinary sill in the art at the time of filing to modify the teaching of Tai and Merten who in teaches the encapsulation of genetically engineered cells to deliver the gene product of interest in vivo, with the teaching of Wei et al who teaches generically engineered cells that produces p450. One would have been motivated to make a capsule containing genetically engineered cells that produces cytochrome p450 because encapsulation of cells to overcome problems associated with somatic gene therapy such as the inability to achieve efficient gene transfers, obtaining sustained level of expression of the transfected gene and the necessity to avoid immunorejection after transplantation" (Office Action, pages 6-7). The Examiner further states that "[o]ne would have been motivated to implant encapsulated cells because systemic P450 is known to activate the inert prodrug, CPA into its cytotoxic metabolites, which would then kill cells in the vicinity of the implanted capsule. The [sic] would have had a reasonable expectation of success at the time of filing based on the results of Wei et al. who showed that the transplantation of cytochrome P450 2B1-producing fibroblasts to mice brains followed by CPA administration prevented meningeal neoplasia as well as the results of Tai et al. that showed significantly higher levels of human growth hormone from the recipients of encapsulated cells relative to the recipients of unencapsulated cells. In addition, one ordinary artisan would have been motivated at the time of filing to also include in the claimed pharmaceutical kit, the prodrug which is activated by cytochrome P450, in a different form because by supplying both components together as a kit, make their intended use easier" (Office Action, page 7).

Applicants respectfully disagree. The combined teachings of Tai *et al.*, Wei *et al.* and Merten *et al.* do not suggest to the person of ordinary skill in the art that they should encapsulate the cytochrome P450 2B1-producing fibroblasts of Wei *et al.* with the capsules of Tai *et al.* and Merten *et al.*, and thus, the combined teaching does not establish a reasonable expectation of success in doing so (*In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991)).

Tai *et al.* describe "immunoisolating genetically modified cells in a biocomptaible membrane, thereby introducing a system that can provide ***sustained delivery*** of the desired gene product" (Tai *et al.*, abstract, emphasis added). Tai *et al.* clearly teach that their system allows "easy diffusion of the secreted gene products" (Tai *et al.*, page 1061, column 2). Tai *et al.* teach that:

> the studies presented here suggest that the encapsulation of genetically modified fibroblasts may represent a useful delivery system for recombinant proteins in vivo. One major advantage of this system is the ease with which the amount of protein to be delivered systematically can be controlled . . . This type of delivery system may be useful in the treatment of a number of diseases where sustained delivery of the missing protein is required (Tai *et al.*, page 1068, columns 1-2).

Thus, Tai *et al.* make clear that ***the gene product should be released from the capsule*** into the environment.

Merten *et al.* developed an encapsulation system in which capsules "were produced using a solution of cellulose phosphate (CS) (1.5%) and poly-dimethyl-diallyl-ammoniumchloride (PDMCAAC)" and tested the "influences of varying encapsulation process parameters on capsule characteristics, cell growth, and monoclonal antibody production" (Merten *et al.*, page 121, abstract).

Wei *et al.* teach that "[m]urine fibroblasts producing a retrovirus vector encoding P450 2B1 and expressing this enzyme were . . . prepared and grafted into the brains of athymic mice seeded with rat C6 gliomas" and that "[i]ntrathecal administration of CPA prevented the development of meningeal neoplasia and led to partial regression of the parenchymal tumor mass" (Wei *et al.* abstract). Wei *et al.* teach that "[i]t is not clear at this time whether the tumor regression mediated by grafting of these cells into the tumor was caused by release of toxic CPA metabolites from P450 2B1-expressing fibroblasts and/or by retrovirus-mediated transfer of the p450 2B1 gene to neighboring tumor cells" and that "[i]n either case, ***it should be possible to transfer the cytochrome P450 2B1 gene into a variety of peripheral and brain tumors*** by using both viral and nonviral vectors" (Wei *et al.*, page 976, column 1, emphasis added). Wei *et al.* teach that their results indicate that "*in situ* conversion of CPA to its active metabolites by neighboring fibroblasts, and ***probably by tumor cells infected with P450 2B1 retrovirus vectors***, dramatically inhibited meningeal tumor spread when the prodrug was administered intrathecally or intratumorally" (Wei *et al.*, page 973, column 2, emphasis added). In addition, Wei *et al.* clearly teach that "***[s]table transfection of rat C6 glioma cells with the P450 2B1 gene*** rendered the cultured tumor cells sensitive to CPA" and that "C6 cells bearing this gene were more sensitive than parental cells to the cytotoxicity action of CPA when grown subcutaneously in the flanks of athymic mice" (Wei *et al.*, abstract, emphasis added).

Applicants' claimed invention relates to a capsule comprising a porous membrane formed by a polyelectrolyte complex which encapsulates a cell which expresses a cytochrome P450 gene, wherein ***the membrane is permeable to prodrug molecules, and the cytochrome P450 gene and the cytochrome P450 expressed by the gene are retained within the capsule***. The claimed invention further relates to the use of the capsules to ablate tumor cells or to treat a tumor.

If one of skill in the art combined the teachings of Tai *et al*, Wei *et al.* and Merten *et al.*, ***stable transfection of tumor cells with the P450 2B1 gene*** as taught by Wei *et al.* ***would not occur*** because, according to Applicant's claimed invention, the cytochrome P450 is retained in the capsule. An obviousness rejection based upon the modification of a reference that destroys the intent, purpose or function of the teaching in the reference is not a proper obviousness rejection (*In re Gordon*, 221 U.S.P.Q. 1125 (Fed. Cir. 1984)).

Furthermore, why would a person of skill in the art add the extra and time consuming step of encapsulating the cytochrome P450 2B1-producing fibroblasts of Wei *et al.*, thereby further complicating the process, when the tumor therapy of Wei *et al.* was successful without the use of capsules? There is no motivation to encapsulate the cytochrome P450 2B1-producing fibroblasts of Wei *et al.*, because there is no indication in the Wei *et al.* reference that problems "associated with somatic gene therapy such as the inability to achieve efficient gene transfers, obtaining sustained level of expression of the transfected gene and the necessity to avoid immunorejection after transplantation" were encountered.

In discussing obviousness, the court has stated that:

> [a]n invention is not obvious merely because it is a combination of old elements each of which was well known in the art at the time the invention was made. . . Rather, if such a combination is novel, the issue is whether bringing them together as taught by the patentee was obvious in light of the prior art. . . The critical inquiry is whether 'there is something in the prior art as a whole to *suggest* the desirability, and thus obviousness of making the invention' (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*13 USPQ2d 1737 at 1765).

That is, the issue is "whether the teachings of the prior art would, *in and of themselves and without the benefit of appellant's disclosure,* make the invention as a whole, obvious" (*In re Sponnoble* 160 USPQ237 at 243 (CCPA 1969)). The combined teachings of Tai *et al.*, Wei *et al.* and Merten *et al.* do not *in and of themselves and without the benefit of applicant's disclosure,*

suggest encapsulatimg cells which express a cytochrome P450 gene in a capsule comprising a porous membrane formed by a polyelectrolyte complex.

The prior art combination of record has been made with the advantage of *impermissible hindsight*, and thus, the rejection is legally improper. That is, in making the obviousness rejection, the Examiner has read the prior art with the benefit of Applicant's disclosure in which there is a clear teaching of the desirability of encapsulatimg cells which express a cytochrome P450 gene in a capsule comprising a porous membrane formed by a polyelectrolyte complex. As the court made clear in *In re Dow*, it is not legally correct to rely on Applicant's disclosure for the suggestion that the cited references should be combined and the expectation of success (*In re Dow Chemical*, 5 U.S.P.Q.2d 1529, 1531-1532 (Fed. Cir. 1988)). In the present case, the suggestion or motivation for combining the references and the expectation of success are not found in the prior art, but rather in Applicant's disclosure.

The combined teachings of Tai *et al.*, Wei *et al.* and Merten *et al.* do not render obvious Applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,
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Dated: June 20, 2002

MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

10. (Twice amended) A method for ablation of tumour cells, comprising [contacting with] administering locally into said tumor cells or close to the site of said tumor cells prodrug molecules and a capsule wherein the capsule comprises a porous membrane formed by a polyelectrolyte complex which encapsulates cells which express a cytochrome P450 gene, wherein the membrane is permeable to the prodrug molecules, the cytochrome P450 gene and the cytochrome P450 expressed by the gene are retained within the capsule and the prodrug molecules are converted into active drug molecules by cytochrome P450 and thereby ablate the tumor cells.